Interferon lambda 3/4 polymorphisms are associated with AIDS-related Kaposi's sarcoma

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Background: Kaposi's sarcoma, the most common AIDS-related cancer, represents a major public concern in resource-limited countries. Single nucleotide polymorphisms within the Interferon lambda 3/4 region (IFNL3/4) determine the expression, function of IFNL4, and influence the clinical course of an increasing number of viral infections.

Objectives: To analyze whether *IFNL3/4* variants are associated with susceptibility to AIDS-related Kaposi's sarcoma among MSM enrolled in the Swiss HIV Cohort Study (SHCS).

Methods: The risk of developing Kaposi's sarcoma according to the carriage of *IFNL3/4* SNPs *rs8099917* and *rs12980275* and their haplotypic combinations was assessed by using cumulative incidence curves and Cox regression models, accounting for relevant covariables.

Results: Kaposi's sarcoma was diagnosed in 221 of 2558 MSM Caucasian SHCS participants. Both *rs12980275* and *rs8099917* were associated with an increased risk of Kaposi's sarcoma (cumulative incidence 15 versus 10%, $P = 0.01$ and 16 versus 10%, $P = 0.009$, respectively). Diplotypes predicted to produce the active P70 form (cumulative incidence 16 versus 10%, $P = 0.01$) but not the less active S70 (cumulative incidence 11 versus 10%, $P = 0.7$) form of IFNL4 were associated with an increased risk of Kaposi's sarcoma, compared with those predicted not to produce IFNL4. The associations remained significant in a multivariate Cox regression model after adjustment for age at infection, combination antiretroviral therapy, median CD4$^+$ T-cell count

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nadir and $CD4^+$ slopes (hazard ratio 1.42, 95% confidence interval 1.06–1.89, $P = 0.02$ for IFLN P70 versus no IFNL4).

Conclusion: This study reports for the first time an association between *IFNL3/4* polymorphisms and susceptibility to AIDS-related Kaposi's sarcoma.

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Introduction

Kaposi's sarcoma was initially described by Moritz Kaposi [1] in 1872 as a rare and relatively indolent angioproliferative neoplasm affecting elderly men from countries surrounding the Mediterranean Sea (classical form of Kaposi's sarcoma). Another form was described in sub-Saharan Africa in the 1950s, which affects middle aged adults and children (endemic form of Kaposi's sarcoma) [2]. In 1981, a potentially fatal form of Kaposi's sarcoma was described among young homosexual men as a characteristic feature of the AIDS epidemics (epidemic form of Kaposi's sarcoma), a population in which it still represents one of the most common AIDS-related cancer [3–8]. An invasive form can also affect patients with non-AIDS immune suppression, in particular, solid organ transplant (SOT) recipients (iatrogenic form of Kaposi's sarcoma, reviewed in [2]).

Although the four epidemiological forms of Kaposi's sarcoma share the same histological characteristics [9] and are all subsequent to human herpes virus 8 (HHV-8) infection [10,11], the development of distinct clinical features seems to rely on a combination of host and environmental factors. Although HIV-related or drug-related immune suppression is inherent to the epidemic and iatrogenic forms (AIDS and SOT), genetic predisposition may be required for the classical (Mediterranean and Jewish ancestry) [12–14] and endemic forms (sub-Saharan Africa) [15]. Hormonal factors [16–19] have been proposed to explain the male predominance of all forms of Kaposi sarcoma. Environmental conditions relative to potential routes of infection (soil, animal vectors) have been proposed to influence susceptibility to different forms of Kaposi's sarcoma [20–25]. Although viral factors may influence clinical presentation, evidence for a definite link between a specific subtype strain and a Kaposi's sarcoma type is still lacking [26–29].

Several investigators have analyzed the role of host genetic factors in susceptibility to Kaposi's sarcoma within a given population at risk. The most relevant was a polymorphism within the *IL-6* promoter, which was consistently more frequent among Kaposi's sarcoma patients versus controls in two cohorts of AIDS patients [30,31] and a small cohort of SOT patients [32]. Polymorphisms in other candidate genes (e.g. MHC-related or cytokines/chemokines-related genes) were associated with Kaposi's sarcoma in studies of AIDS patients [31,33–35] and two studies including patients with the classical form of Kaposi's sarcoma [36,37].

Single nucleotide polymorphisms (SNPs) in the region encoding for interferon lambda 3 (IFNL3 previously named IL-28B) and interferon lambda 4 (*IFNL4*) represent major factors in the ability of individuals to clear hepatitis C virus (HCV) [38–41]. They determine different haplotypic combinations (diplotypes) based on their capacity to produce IFNL4, that is, no production versus production as an active P70 or less active S70 form [42–44]. *IFNL3/4* SNPs are increasingly known to influence the susceptibility to or the clinical course of infections due to viruses other than HCV, including herpes viruses such as cytomegalovirus (CMV) and Epstein–Barr virus (EBV) [45–47]. Here, we hypothesize that *IFNL3/4* polymorphisms influence the risk of AIDS patients to develop Kaposi's sarcoma.

Material and methods

Study patients

The Swiss HIV Cohort Study (SHCS) is an ongoing multicenter prospective study of HIV-infected patients enrolled at seven major Swiss hospitals and their local affiliated centers since 1988 [48]. For the present study, Caucasian MSM with available DNA for genotyping and a written informed consent for genetic studies were included. In order to account for the time at risk, only patients with an estimated date of HIV infection were selected [49]. Demographic characteristics including age, duration of HIV infection, $CD4^+$ T-cell count nadir, other opportunistic infections, HIV maximal viral load and HAART use were extracted from the SHCS clinical database. Kaposi's sarcoma was defined according to predefined clinical and histological criteria.

Single nucleotide polymorphism genotyping

Genomic DNA isolated either from blood or cell pellets was genotyped for haplotype tagging SNPs *rs8099917* and *rs12980275* using a customized GoldenGate

Genotyping Assay on Veracode platform (Illumina , San Diego, California, USA). These SNPs were used as surrogates for rs368234815 and rs117648444, respectively, based on previously published linkage disequilibrium (LD) values, which were shown to determine the three main diplotypic forms of IFNL4.

Statistical analysis

Statistical analyses were performed using Stata (version 14.2, StataCorp LP, College Station, Texas, USA). Hardy–Weinberg equilibrium (HWE) was verified using the program genhw implemented in Stata. Haplotypes were inferred using Phase and grouped according to their ability to express the different forms of IFNL3/4 as described previously [43]. The association of *IFNL3/4* polymorphisms with Kaposi's sarcoma was assessed by 25-year cumulative incidence curves as well as univariable and multivariable Cox regression models, using the estimated date of HIV infection as a starting point, with censoring at death and/or lost follow-up. The proportional hazard assumption was verified by using the stphtest command implemented in Stata. Estimated dates of HIV infection and $CD4^+$ slopes in both incident and prevalent cases were obtained by using a joint back calculation model as described previously [50].

Results

The study included 2558 MSM patients among whom 221 developed Kaposi's sarcoma (8.6%, Supplementary Table 1, http://links.lww.com/QAD/B360). Considering the whole patient population, the median age at estimated date of HIV infection was 34 (interquartile range, IQR = 13). The median $CD4^+$ T-cell nadir was 181 cells/mm^3 (IQR = 174) and the maximal HIV RNA viral load 5.12 $\log_{10}$ copies/ml (IQR = 0.85). Most individuals started HAART therapy during follow-up (97%). An active HBV infection was recorded in 10% of patients and HCV serology was positive in 8%.

The minor allele frequencies (MAFs) of IFNL3/4 *rs12980275* and *rs8099917* were 0.30 and 0.20, respectively, and both were at HWE. Carriage of *rs12980275* and *rs8099917* were both associated with an increased risk of Kaposi's sarcoma (cumulative incidence 15 versus 10%, $P = 0.01$ and cumulative incidence 16 versus 10%, $P = 0.009$, respectively, Fig. 1). Diplotypes predicted to produce the active P70 form of IFNL4, but not those predicted to produce the less active S70 form were associated with an increased risk of Kaposi's sarcoma, compared with diplotypes not producing IFNL4 (cumulative incidence 16 versus 10%, $P = 0.01$ and cumulative incidence 11 versus 10%, $P = 0.7$, respectively).

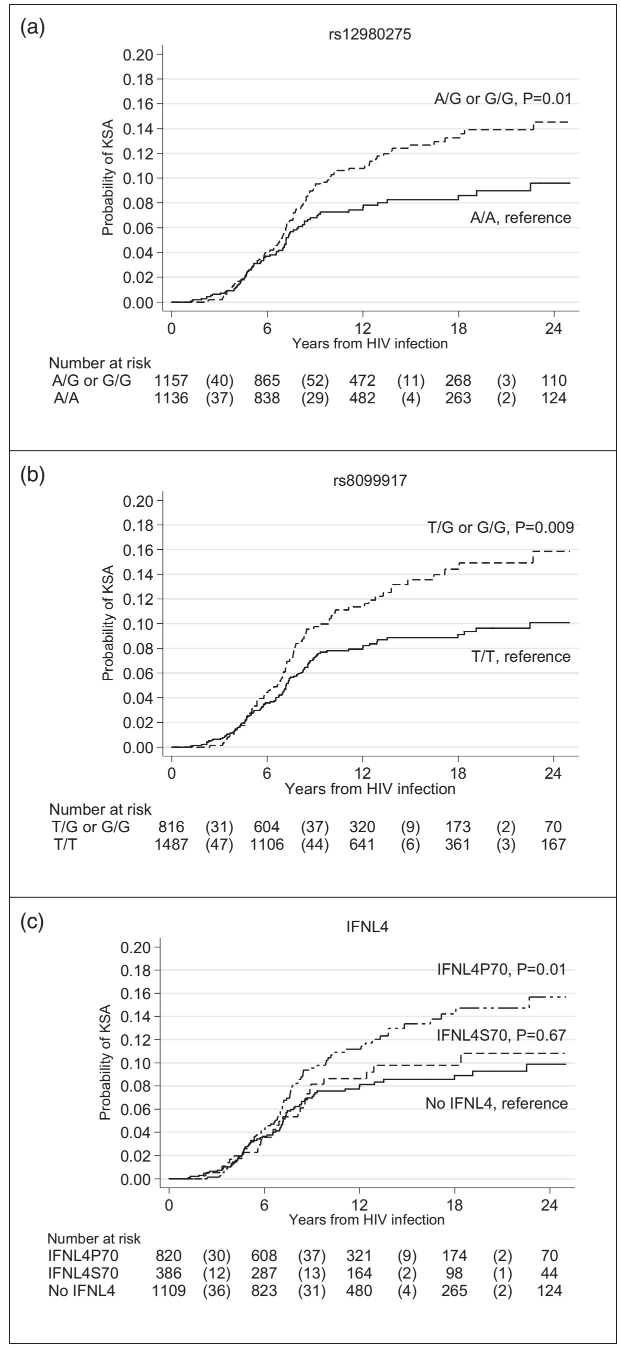

Fig. 1. Cumulative incidence of Kaposi's sarcoma according to IFNL4 *rs12980275* (a), IFNL3/4 *rs8099917* (b), IFNL4 diplotypes (c) in MSM participants of the Swiss HIV Cohort Study. The estimated date of HIV infection was used as a starting point with censoring at death or lost follow-up. Numbers in parenthesis indicate the number of patients with Kaposi's sarcoma in each group of patients. *P* values were calculated by log-rank test, dominant mode.

The association between IFNL4P70-producing diplotypes and Kaposi's sarcoma remained significant in a multivariate Cox regression model, accounting for age at infection, HAART, median $CD4^+$ T-cell count nadir and

Table 1. Independent risk factors associated with Kaposi's sarcoma among MSM.

	Univariate		Multivariate	
Variable	Hazard ratio (95% CI)[a]	P	Hazard ratio (95% CI)	P
Age at estimated date of infection[b]	1.01 (1.00–1.03)	0.07	1.01 (1.00–1.03)	0.04
$CD4^+$ nadir (<200 cells/mm^3)	2.56 (1.87–3.51)	<0.001	2.02 (1.45–2.82)	<0.001
$CD4^+$ slope[c] (continuous)	0.69 (0.58–0.81)	<0.001	0.71 (0.60–0.85)	<0.001
Maximal HIV RNA load (continuous)	1.21 (1.01–1.44)	0.04		
HAART (time-dependant covariate)	0.43 (0.31–0.60)	<0.001	0.36 (0.25–0.51)	<0.001
HCV co-infection[d]	0.92 (0.55–1.53)	0.75		
Active HBV infection[e]	1.32 (0.78–2.24)	0.30		
SNPs				
IFNL3/4 rs12980275 (AA versus AG or GG)	1.36 (1.04–1.77)	0.03		
IFNL3/4 rs8099917 (TT versus TG or GG)	1.40 (1.07–1.82)	0.01		
Diplotypes				
No IFNL4	Reference		Reference	
IFNL4 P70	1.40 (1.05–1.87)	0.02	1.42 (1.06–1.89)	0.02
IFNL4 S70	1.09 (0.74–1.61)	0.67	1.11 (0.75–1.64)	0.61

CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus.
[a]The proportional hazard assumption was verified for all variables with the exception of $CD4^+$ slope. However, the association between IFNL4P70 and Kaposi's sarcoma was similar when $CD4^+$ slope was removed from the multivariate model (hazard ratio 1.33, 95% CI 1.07–1.65, $P=0.01$).
[b]Per 1 year.
[c]Rate of $CD4^+$ depletion in the absence of HAART.
[d]Reflected by HCV serology.
[e]Defined by the presence of HBsAg in the blood.

$CD4^+$ slopes (hazard ratio 1.42, 95% confidence interval (95% CI) 1.06–1.89, $P=0.02$; Table 1).

Discussion

Polymorphisms in the region encoding for IFNL3 and 4 have been identified for their major role in the ability of individuals to clear HCV. Increasing evidence suggests that such polymorphisms can also influence the clinical course of infections due to viruses other than HCV [51,52], in particular those from the Herpesviridae family [CMV [45,46], EBV [47] and herpes simplex virus (HSV) [53]]. In this study, we report for the first time an association between *IFNL3/4* polymorphisms and susceptibility to Kaposi's sarcoma among HIV-infected MSM.

An increasing number of in-vitro studies support the role of IFNL in the immunopathogenesis of viral infections due to viruses other than HCV. A series of cell culture-based models have shown that IFNL3/4 controls the replication of viruses such as human [54] and murine CMV [55], HSV2 [56], HBV [57], dengue virus [58], human metapneumovirus (hMPV) [59], influenza virus [60–62], lymphocytic choriomeningitis virus (LCMV) [63] and Sendai virus [64]. Although no studies have analyzed the direct role of IFNL on HHV-8 replication, the involvement of IFNL in its immunopathogenesis is supported indirectly by at least two studies. Those showed that HHV-8 can inhibit interferon transcription by the production of interferon regulatory factor (IRF) homologues as well as block the expression of interferon-stimulating genes (ISGs) through Janus kinase-signal transducer and activator of transcription pathway interference [65,66].

Haplotypic combinations predicted to produce the P70 active, but not the S70 less active form of IFNL4, were associated with an increased risk of Kaposi's sarcoma. This is consistent with the association reported in other viral infections; SNPs encoding or tagging the P70 form of IFNL4 induce a higher susceptibility to HCV [42,44], CMV [45,46], EBV [47] and HSV [53]. This paradoxical effect of IFNL4 may rely on at least three different mechanisms. First, IFNL4 may compete with the other IFNLs through a mechanism involving the overexpression of its IFNLR1 subunit [67]. Second, IFNL4 may induce a refractory state of the pathway because of persistent ISG expression [43]. Third, individuals expressing the active form of IFNL4 may in return produce lower amount of IFNL3, with subsequent reduced ISG expression [42,68,69]. The resulting balance between IFNL3 and IFNL4 expression may be particularly relevant in Kaposi's sarcoma lesions, given the presence of numerous recruited plasmacytoid dendritic cells (pDC), which represent the most important producer of these cytokines [70].

Beyond antiviral properties, IFNLs may also exert antitumoral activities including a growth inhibitory effect and apoptosis of tumor cells, as recently described in culture of melanoma [71], lung adenocarcinoma [72,73], neuroendocrine cancer [74], colorectal carcinoma [75], esophageal carcinoma [76] and hepatocellular carcinoma [77] cells or in mouse models of melanoma [78], colon adenocarcinoma [78] and fibrosarcoma [79]. In humans, the expression of IFNL1 has been negatively correlated with the progression of cervical cancer because of papilloma virus [80], suggesting a potential role of this cytokine in cancer immunity. Altogether, these data suggest that polymorphisms in IFNLs may not only influence the immunity against HHV-8, but also the immunity against Kaposi's sarcoma cancer cells.

Like most genetic association studies, our study performed on HIV-infected MSM is constrained by some limitations. Data on HHV-8 seroprevalence are not available in the SHCS cohort, thereby preventing analyses limited to patients with Kaposi's sarcoma but excluding HHV-8-positive individuals who did not develop Kaposi's sarcoma. This limitation may be at least in part compensated by the fact that the prevalence of HHV-8 among MSM is elevated [81,82] and that the prevalence of Kaposi's sarcoma and HHV-8 is very well correlated in HIV-infected populations [83–85]. Most likely, the currently chosen analytic approach would underestimate but not overestimate the effect of IFNL polymorphisms.

In summary, our data show an association between *IFNL3/4* polymorphisms and the development of Kaposi's sarcoma among HIV+ MSM patients. This new finding confirms that IFNLs mediate antiviral responses against a growing range of viruses.

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Conflicts of interest

There are no conflicts of interest.

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Author's contributions

S.B. performed sample management, DNA extraction, candidate SNP genotyping, statistical analysis and wrote the manuscript. A.W. performed SNP genotyping for the SHCS patients and data management. P.T. contributed to statistical analyses. Members of the SHCS group including, P.E.T., E.B., H.F., H.F.G., M.H., L.K., M.O., J.F., M.C. were directly involved in the clinical care of SHCS patients and data acquisition. P.Y.B. designed the SHCS genetic project, obtained funding, supervised genotyping, performed data management and statistical analysis and wrote the manuscript. All authors critically revised the manuscript.

References

1. Kaposi M. **Idiopathisches multiples Pigmentsarcom der Haut.** *Arch Dermatol Syphilol* 1872; **4**:265.
2. Mesri EA, Cesarman E, Boshoff C. **Kaposi's sarcoma and its associated herpesvirus.** *Nat Rev Cancer* 2010; **10**:707–719.
3. Goedert JJ. **The epidemiology of acquired immunodeficiency syndrome malignancies.** *Semin Oncol* 2000; **27**:390–401.
4. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. **Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis.** *Lancet* 2007; **370**:59–67.
5. Ledergerber B, Telenti A, Egger M. **Risk of HIV related Kaposi's sarcoma and non-Hodgkin's lymphoma with potent antiretroviral therapy: prospective cohort study. Swiss HIV Cohort Study.** *BMJ* 1999; **319**:23–24.
6. Ledergerber B, Egger M, Erard V, Weber R, Hirschel B, Furrer H, *et al.* **AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study.** *JAMA* 1999; **282**:2220–2226.
7. Franceschi S, Maso LD, Rickenbach M, Polesel J, Hirschel B, Cavassini M, *et al.* **Kaposi sarcoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy.** *Br J Cancer* 2008; **99**:800–804.
8. Sullivan SG, Hirsch HH, Franceschi S, Steffen I, Amari EB, Mueller NJ, *et al.* **Kaposi sarcoma herpes virus antibody response and viremia following highly active antiretroviral therapy in the Swiss HIV Cohort study.** *AIDS* 2010; **24**:2245–2252.
9. Ablashi DV, Chatlynne LG, Whitman JE Jr, Cesarman E. **Spectrum of Kaposi's sarcoma-associated herpesvirus, or human herpesvirus 8, diseases.** *Clin Microbiol Rev* 2002; **15**:439–464.
10. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, *et al.* **Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma.** *Science* 1994; **266**:1865–1869.
11. Russo JJ, Bohenzky RA, Chien MC, Chen J, Yan M, Maddalena D, *et al.* **Nucleotide sequence of the Kaposi sarcoma-associated herpesvirus (HHV8).** *Proc Natl Acad Sci U S A* 1996; **93**:14862–14867.
12. Camcioglu Y, Picard C, Lacoste V, Dupuis S, Akcakaya N, Cokura H, *et al.* **HHV-8-associated Kaposi sarcoma in a child with IFNgammaR1 deficiency.** *J Pediatr* 2004; **144**:519–523.
13. Byun M, Abhyankar A, Lelarge V, Plancoulaine S, Palanduz A, Telhan L, *et al.* **Whole-exome sequencing-based discovery of STIM1 deficiency in a child with fatal classic Kaposi sarcoma.** *J Exp Med* 2010; **207**:2307–2312.
14. Byun M, Ma CS, Akcay A, Pedergnana V, Palendira U, Myoung J, *et al.* **Inherited human OX40 deficiency underlying classic Kaposi sarcoma of childhood.** *J Exp Med* 2013; **210**:1743–1759.
15. Aavikko M, Kaasinen E, Nieminen JK, Byun M, Donner I, Mancuso R, *et al.* **Whole-genome sequencing identifies STAT4 as a putative susceptibility gene in classic Kaposi sarcoma.** *J Infect Dis* 2015; **211**:1842–1851.
16. Ziegler JL, Katongole-Mbidde E, Wabinga H, Dollbaum CM. **Absence of sex-hormone receptors in Kaposi's sarcoma.** *Lancet* 1995; **345**:925.
17. Klein SL. **The effects of hormones on sex differences in infection: from genes to behavior.** *Neurosci Biobehav Rev* 2000; **24**:627–638.
18. Bouscarat F, Dazza MC, Melchior JC, Bouvet E. **Kaposi's sarcoma and sex hormones.** *AIDS* 1997; **11**:687–688.
19. Lunardi-Iskandar Y, Bryant JL, Blattner WA, Hung CL, Flamand L, Gill P, *et al.* **Effects of a urinary factor from women in early pregnancy on HIV-1, SIV and associated disease.** *Nat Med* 1998; **4**:428–434.
20. Ascoli V, Zambon P, Manno D, Guzzinati S, Zorzi M, Arca B, *et al.* **Variability in the incidence of classic Kaposi's sarcoma in the Veneto region, Northern Italy.** *Tumori* 2003; **89**:122–124.
21. Cook-Mozaffari P, Newton R, Beral V, Burkitt DP. **The geographical distribution of Kaposi's sarcoma and of lymphomas in Africa before the AIDS epidemic.** *Br J Cancer* 1998; **78**:1521–1528.

22. Ziegler JL. **Endemic Kaposi's sarcoma in Africa and local volcanic soils.** *Lancet* 1993; **342**:1348–1351.
23. Montella M, Franceschi S, Geddes M, Arniani S, Cocchiarella G. **Classic Kaposi's sarcoma and volcanic soil in southern Italy.** *Lancet* 1996; **347**:905.
24. Simonart T. **Role of environmental factors in the pathogenesis of classic and African-endemic Kaposi sarcoma.** *Cancer Lett* 2006; **244**:1–7.
25. Henke-Gendo C, Schulz TF. **Transmission and disease association of Kaposi's sarcoma-associated herpesvirus: recent developments.** *Curr Opin Infect Dis* 2004; **17**:53–57.
26. Hsu YH, Kuo WL, Su IJ. **Clinicopathologic study of Kaposi's sarcoma and strain analysis of human herpesvirus 8 (HHV-8) DNA in the Hua-Lien area of eastern Taiwan.** *J Formos Med Assoc* 2001; **100**:449–454.
27. Kakoola DN, Sheldon J, Byabazaire N, Bowden RJ, Katongole-Mbidde E, Schulz TF, *et al*. **Recombination in human herpesvirus-8 strains from Uganda and evolution of the K15 gene.** *J Gen Virol* 2001; **82 (Pt 10)**:2393–2404.
28. Lacoste V, Judde JG, Briere J, Tulliez M, Garin B, Kassa-Kelembho E, *et al*. **Molecular epidemiology of human herpesvirus 8 in Africa: both B and A5 K1 genotypes, as well as the M and P genotypes of K14.1/K15 loci, are frequent and widespread.** *Virology* 2000; **278**:60–74.
29. Stebbing J, Wilder N, Ariad S, Abu-Shakra M. **Lack of intra-patient strain variability during infection with Kaposi's sarcoma-associated herpesvirus.** *Am J Hematol* 2001; **68**:133–134.
30. Foster CB, Lehrnbecher T, Samuels S, Stein S, Mol F, Metcalf JA, *et al*. **An IL6 promoter polymorphism is associated with a lifetime risk of development of Kaposi sarcoma in men infected with human immunodeficiency virus.** *Blood* 2000; **96**:2562–2567.
31. Aissani B, Wiener HW, Zhang K, Kaslow RA, Ogwaro KM, Shrestha S, *et al*. **A candidate gene approach for virally induced cancer with application to HIV-related Kaposi's sarcoma.** *Int J Cancer* 2014; **134**:397–404.
32. Gazouli M, Zavos G, Papaconstantinou I, Lukas JC, Zografidis A, Boletis J, *et al*. **The interleukin-6-174 promoter polymorphism is associated with a risk of development of Kaposi's sarcoma in renal transplant recipients.** *Anticancer Res* 2004; **24 (2C)**:1311–1314.
33. Gaya A, Esteve A, Casabona J, McCarthy JJ, Martorell J, Schulz TF, *et al*. **Amino acid residue at position 13 in HLA-DR beta chain plays a critical role in the development of Kaposi's sarcoma in AIDS patients.** *AIDS* 2004; **18**:199–204.
34. Aissani B, Boehme AK, Wiener HW, Shrestha S, Jacobson LP, Kaslow RA. **SNP screening of central MHC-identified HLA-DMB as a candidate susceptibility gene for HIV-related Kaposi's sarcoma.** *Genes Immun* 2014; **15**:424–429.
35. Lehrnbecher TL, Foster CB, Zhu S, Venzon D, Steinberg SM, Wyvill K, *et al*. **Variant genotypes of FcgammaRIIIA influence the development of Kaposi's sarcoma in HIV-infected men.** *Blood* 2000; **95**:2386–2390.
36. Brown EE, Fallin D, Ruczinski I, Hutchinson A, Staats B, Vitale F, *et al*. **Associations of classic Kaposi sarcoma with common variants in genes that modulate host immunity.** *Cancer Epidemiol Biomarkers Prev* 2006; **15**:926–934.
37. Tornesello ML, Buonaguro L, Cristillo M, Biryahwaho B, Downing R, Hatzakis A, *et al*. **MDM2 and CDKN1A gene polymorphisms and risk of Kaposi's sarcoma in African and Caucasian patients.** *Biomarkers* 2011; **16**:42–50.
38. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, *et al*. **Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance.** *Nature* 2009; **461**:399–401.
39. Suppiah V, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, *et al*. **IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy.** *Nat Genet* 2009; **41**:1100–1104.
40. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, *et al*. **Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C.** *Nat Genet* 2009; **41**:1105–1109.
41. Rauch A, Kutalik Z, Descombes P, Cai T, Di Iulio J, Mueller T, *et al*. **Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study.** *Gastroenterology* 2010; **138**:1338.e1–1345.e7.
42. Bibert S, Roger T, Calandra T, Bochud M, Cerny A, Semmo N, *et al*., Swiss Hepatitis C Cohort Study. **IL28B expression depends on a novel TT/-G polymorphism which improves HCV clearance prediction.** *J Exp Med* 2013; **210**:1109–1116.
43. Terczynska-Dyla E, Bibert S, Duong FH, Krol I, Jorgensen S, Collinet E, *et al*. **Reduced IFNlambda4 activity is associated with improved HCV clearance and reduced expression of interferon-stimulated genes.** *Nat Commun* 2014; **5**:5699.
44. Prokunina-Olsson L, Muchmore B, Tang W, Pfeiffer RM, Park H, Dickensheets H, *et al*. **A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus.** *Nat Genet* 2013; **45**:164–171.
45. Manuel O, Wojtowicz A, Bibert S, Mueller NJ, van Delden C, Hirsch HH, *et al*., Swiss Transplant Cohort Study. **Influence of IFNL3/4 polymorphisms on the incidence of cytomegalovirus infection after solid-organ transplantation.** *J Infect Dis* 2015; **211**:906–914.
46. Bibert S, Wojtowicz A, Taffe P, Manuel O, Bernasconi E, Furrer H, *et al*., Swiss HIV Cohort Study. **The IFNL3/4 DeltaG variant increases susceptibility to cytomegalovirus retinitis among HIV-infected patients.** *AIDS* 2014; **28**:1885–1889.
47. Akay E, Patel M, Conibear T, Chaggar T, Haque T. **Interleukin 28B gene polymorphisms and Epstein-Barr virus-associated lymphoproliferative diseases.** *Intervirology* 2014; **57**:112–115.
48. Swiss HIV Cohort Study. Schoeni-Affolter F, Ledergerber B, Rickenbach M, Rudin C, Gunthard HF, *et al*. **Cohort profile: the Swiss HIV Cohort study.** *Int J Epidemiol* 2010; **39**:1179–1189.
49. Taffe P, May M, Swiss HIV Cohort Study. **A joint back calculation model for the imputation of the date of HIV infection in a prevalent cohort.** *Stat Med* 2008; **27**:4835–4853.
50. Loeuillet C, Deutsch S, Ciuffi A, Robyr D, Taffe P, Munoz M, *et al*. **In vitro whole-genome analysis identifies a susceptibility locus for HIV-1.** *PLoS biology* 2008; **6**:e32.
51. Trevino A, Lopez M, Vispo E, Aguilera A, Ramos JM, Benito R, *et al*., HTLV Spanish Study Group. **Development of tropical spastic paraparesis in human T-lymphotropic virus type 1 carriers is influenced by interleukin 28B gene polymorphisms.** *Clin Infect Dis* 2012; **55**:e1–e4.
52. Angulo J, Pino K, Echeverria-Chagas N, Marco C, Martinez-Valdebenito C, Galeno H, *et al*. **Association of single-nucleotide polymorphisms in IL28B, but not TNF-alpha, with severity of disease caused by Andes virus.** *Clin Infect Dis* 2015; **61**:e62–e69.
53. Griffiths SJ, Koegl M, Boutell C, Zenner HL, Crump CM, Pica F, *et al*. **A systematic analysis of host factors reveals a Med23-interferon-lambda regulatory axis against herpes simplex virus type 1 replication.** *PLoS Pathog* 2013; **9**:e1003514.
54. Egli A, Levin A, Santer DM, Joyce M, O'Shea D, Thomas BS, *et al*. **Immunomodulatory function of interleukin 28B during primary infection with cytomegalovirus.** *J Infect Dis* 2014; **210**:717–727.
55. Brand S, Beigel F, Olszak T, Zitzmann K, Eichhorst ST, Otte JM, *et al*. **IL-28A and IL-29 mediate antiproliferative and antiviral signals in intestinal epithelial cells and murine CMV infection increases colonic IL-28A expression.** *Am J Physiol Gastrointest Liver Physiol* 2005; **289**:G960–G968.
56. Zhou L, Li JL, Zhou Y, Liu JB, Zhuang K, Gao JF, *et al*. **Induction of interferon-lambda contributes to TLR3 and RIG-I activation-mediated inhibition of herpes simplex virus type 2 replication in human cervical epithelial cells.** *Mol Hum Reprod* 2015; **21**:917–929.
57. Robek MD, Boyd BS, Chisari FV. **Lambda interferon inhibits hepatitis B and C virus replication.** *J Virol* 2005; **79**:3851–3854.
58. Palma-Ocampo HK, Flores-Alonso JC, Vallejo-Ruiz V, Reyes-Leyva J, Flores-Mendoza L, Herrera-Camacho I, *et al*. **Interferon lambda inhibits dengue virus replication in epithelial cells.** *Virol J* 2015; **12**:150.
59. Banos-Lara Mdel R, Harvey L, Mendoza A, Simms D, Chouljenko VN, Wakamatsu N, *et al*. **Impact and regulation of lambda interferon response in human metapneumovirus infection.** *J Virol* 2015; **89**:730–742.
60. Mordstein M, Kochs G, Dumoutier L, Renauld JC, Paludan SR, Klucher K, *et al*. **Interferon-lambda contributes to innate immunity of mice against influenza A virus but not against hepatotropic viruses.** *PLoS pathogens* 2008; **4**:e1000151.

61. Mordstein M, Neugebauer E, Ditt V, Jessen B, Rieger T, Falcone V, *et al*. **Lambda interferon renders epithelial cells of the respiratory and gastrointestinal tracts resistant to viral infections.** *J Virol* 2010; **84**:5670–5677.
62. Jewell NA, Cline T, Mertz SE, Smirnov SV, Flano E, Schindler C, *et al*. **Lambda interferon is the predominant interferon induced by influenza A virus infection in vivo.** *J Virol* 2010; **84**:11515–11522.
63. Lukacikova L, Oveckova I, Betakova T, Laposova K, Polcicova K, Pastorekova S, *et al*. **Antiviral effect of interferon lambda against lymphocytic choriomeningitis virus.** *J Interferon Cytokine Res* 2015; **35**:540–553.
64. Ank N, West H, Bartholdy C, Eriksson K, Thomsen AR, Paludan SR. **Lambda interferon (IFN-lambda), a type III IFN, is induced by viruses and IFNs and displays potent antiviral activity against select virus infections in vivo.** *J Virol* 2006; **80**:4501–4509.
65. Wen KW, Damania B. **Kaposi sarcoma-associated herpesvirus (KSHV): molecular biology and oncogenesis.** *Cancer Lett* 2010; **289**:140–150.
66. Djerbi M, Screpanti V, Catrina AI, Bogen B, Biberfeld P, Grandien A. **The inhibitor of death receptor signaling, FLICE-inhibitory protein defines a new class of tumor progression factors.** *J Exp Med* 1999; **190**:1025–1032.
67. Duong FH, Trincucci G, Boldanova T, Calabrese D, Campana B, Krol I, *et al*. **IFN-lambda receptor 1 expression is induced in chronic hepatitis C and correlates with the IFN-lambda3 genotype and with nonresponsiveness to IFN-alpha therapies.** *J Exp Med* 2014; **211**:857–868.
68. Honda M, Shirasaki T, Shimakami T, Sakai A, Horii R, Arai K, *et al*. **Hepatic interferon-stimulated genes are differentially regulated in the liver of chronic hepatitis C patients with different interleukin-28B genotypes.** *Hepatology* 2014; **59**:828–838.
69. Fukuhara T, Taketomi A, Motomura T, Okano S, Ninomiya A, Abe T, *et al*. **Variants in IL28B in liver recipients and donors correlate with response to peg-interferon and ribavirin therapy for recurrent hepatitis C.** *Gastroenterology* 2010; **139**:1577–158585 e1-3.
70. Karouni M, Kurban M, Abbas O. **Plasmacytoid dendritic cells in skin lesions of classic Kaposi's sarcoma.** *Arch Dermatol Res* 2016; **308**:487–492.
71. Lasfar A, Lewis-Antes A, Smirnov SV, Anantha S, Abushahba W, Tian B, *et al*. **Characterization of the mouse IFN-lambda ligand-receptor system: IFN-lambdas exhibit antitumor activity against B16 melanoma.** *Cancer Res* 2006; **66**:4468–4477.
72. Tezuka Y, Endo S, Matsui A, Sato A, Saito K, Semba K, *et al*. **Potential antitumor effect of IFN-lambda2 (IL-28A) against human lung cancer cells.** *Lung cancer* 2012; **78**:185–192.
73. Yan Y, Zhang J, Liu Y, Zhu T, Yuan L, Ge Y, *et al*. **Inhibition of lung adenocarcinoma transfected with interleukin 28A recombinant adenovirus (Ad-mIFN-lambda2) in vivo.** *Cancer Biother Radiopharm* 2013; **28**:124–130.
74. Zitzmann K, Brand S, Baehs S, Goke B, Meinecke J, Spottl G, *et al*. **Novel interferon-lambdas induce antiproliferative effects in neuroendocrine tumor cells.** *Biochem Biophys Res Commun* 2006; **344**:1334–1341.
75. Hui X, Chen H, Zhang S, Ma X, Wang X, Huang B. **Antitumor activities of recombinant human interferon (IFN)-lambda1 in vitro and in xenograft models in vivo for colon cancer.** *Cancer Lett* 2011; **311**:141–151.
76. Li Q, Kawamura K, Ma G, Iwata F, Numasaki M, Suzuki N, *et al*. **Interferon-lambda induces G1 phase arrest or apoptosis in oesophageal carcinoma cells and produces antitumour effects in combination with anticancer agents.** *Eur J Cancer* 2010; **46**:180–190.
77. Abushahba W, Balan M, Castaneda I, Yuan Y, Reuhl K, Raveche E, *et al*. **Antitumor activity of type I and type III interferons in BNL hepatoma model.** *Cancer Immunol Immunother* 2010; **59**:1059–1071.
78. Sato A, Ohtsuki M, Hata M, Kobayashi E, Murakami T. **Antitumor activity of IFN-lambda in murine tumor models.** *J Immunol* 2006; **176**:7686–7694.
79. Numasaki M, Tagawa M, Iwata F, Suzuki T, Nakamura A, Okada M, *et al*. **IL-28 elicits antitumor responses against murine fibrosarcoma.** *J Immunol* 2007; **178**:5086–5098.
80. Cannella F, Scagnolari C, Selvaggi C, Stentella P, Recine N, Antonelli G, *et al*. **Interferon lambda 1 expression in cervical cells differs between low-risk and high-risk human papillomavirus-positive women.** *Med Microbiol Immunol* 2014; **203**:177–184.
81. Regamey N, Cathomas G, Schwager M, Wernli M, Harr T, Erb P. **High human herpesvirus 8 seroprevalence in the homosexual population in Switzerland.** *J Clin Microbiol* 1998; **36**:1784–1786.
82. Liu Z, Fang Q, Zuo J, Chen Y, Minhas V, Wood C, *et al*. **Global epidemiology of human herpesvirus 8 in men who have sex with men: a systematic review and meta-analysis.** *J Med Virol* 2018; **90**:582–591.
83. Gao SJ, Kingsley L, Li M, Zheng W, Parravicini C, Ziegler J, *et al*. **KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma.** *Nat Med* 1996; **2**:925–928.
84. Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes DH. **Sexual transmission and the natural history of human herpesvirus 8 infection.** *N Engl J Med* 1998; **338**:948–954.
85. Simpson GR, Schulz TF, Whitby D, Cook PM, Boshoff C, Rainbow L, *et al*. **Prevalence of Kaposi's sarcoma associated herpesvirus infection measured by antibodies to recombinant capsid protein and latent immunofluorescence antigen.** *Lancet* 1996; **348**:1133–1138.

Appendix

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